# 後中醫學系藥理學

義大醫院免疫風濕科王世緯

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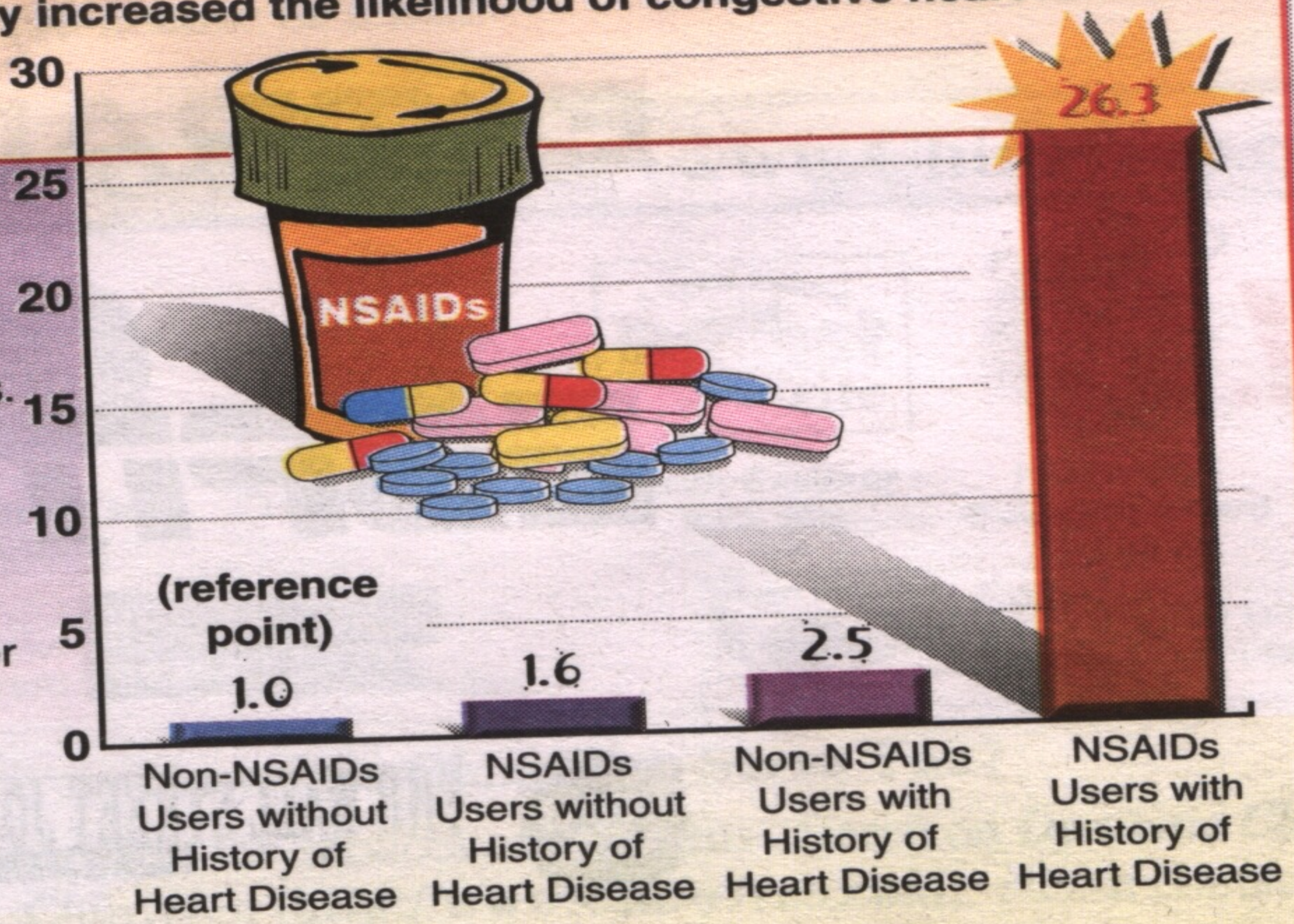
# NSAIDs Bad for Older Hearts

**A recent study[1] showed the use of nonsteroidal anti-inflammatory drugs (NSAIDs) dramatically increased the likelihood of congestive heart failure in elderly patients:**

Every year in the U.S., an estimated 7,600 people (mostly the elderly) die from the effects of NSAIDs. Gastrointestinal bleeding and perforation account for one death for every 9,210 prescriptions; another 76,000 end up in the hospital (one hopitalization for every 921 prescriptions.[2]





1. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients. *Arch Intern Med* 2000;160:777-784.

2. Tamblyn R, Berkson L, Dauphinee WD, et al. Unnecessary prescribing of NSAIDs and the management of NSAID-related gastropathy in medical practice. *Ann Intern Med* 1997;127:429-438.

# 解熱性止痛劑 (Non-steroid anti-inflammatory drug; NSAID)

- 具有止痛、退熱和抗發炎的功能，為非類固醇消炎止痛藥
- 止痛效果較麻醉性止痛劑弱
- 不具成癮性
- 不會產生呼吸抑制作用

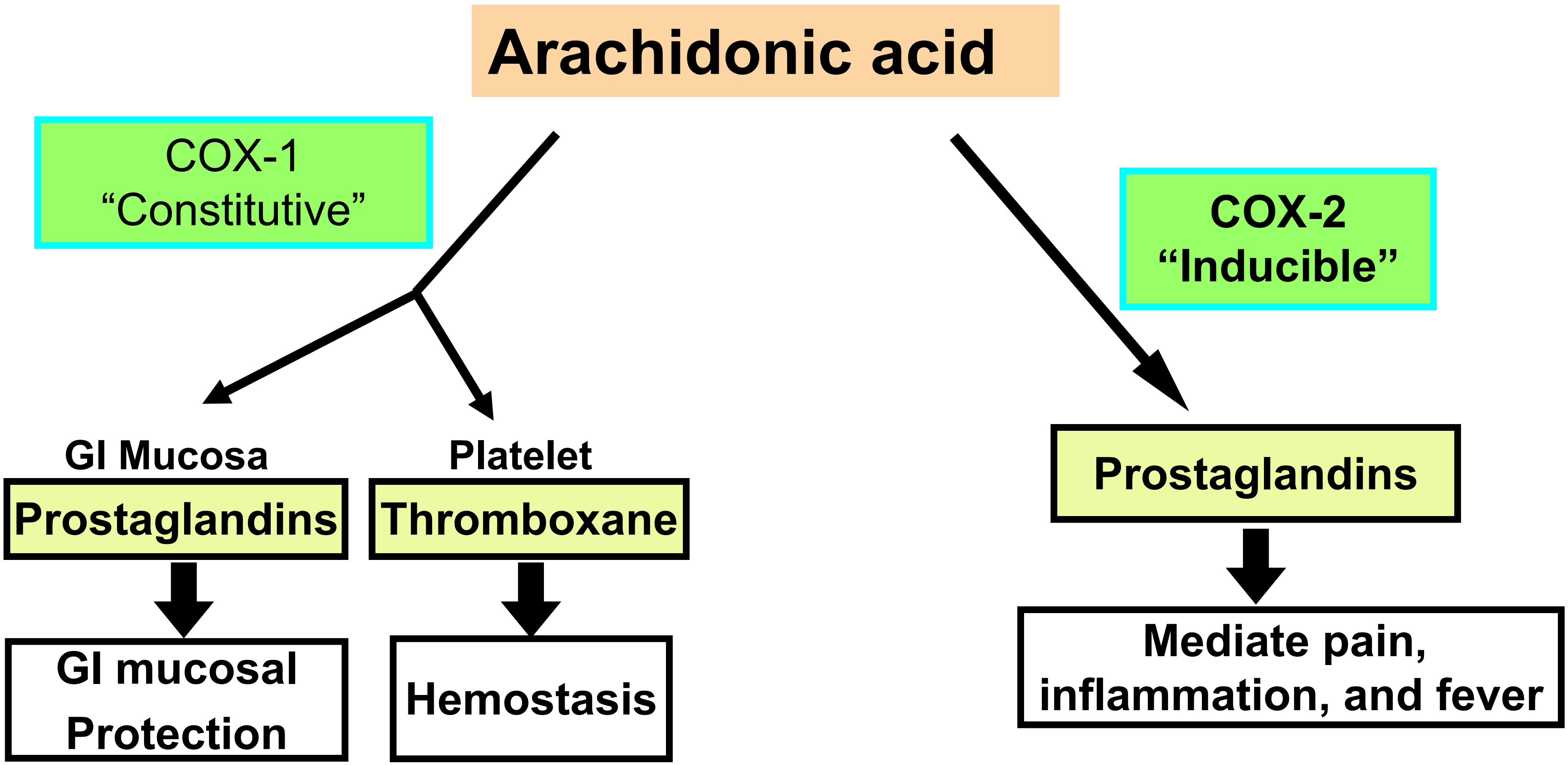
# 解熱性止痛劑
## 止痛作用機轉

- 在中樞系統及周邊產生止痛作用(對週邊的作用較重
- 作用來自抑制發炎組織前列腺素的合成，因此降低發炎媒介物如histamine、bradykinin所造成的疼痛
- 止痛作用與抗發炎作用有關聯性

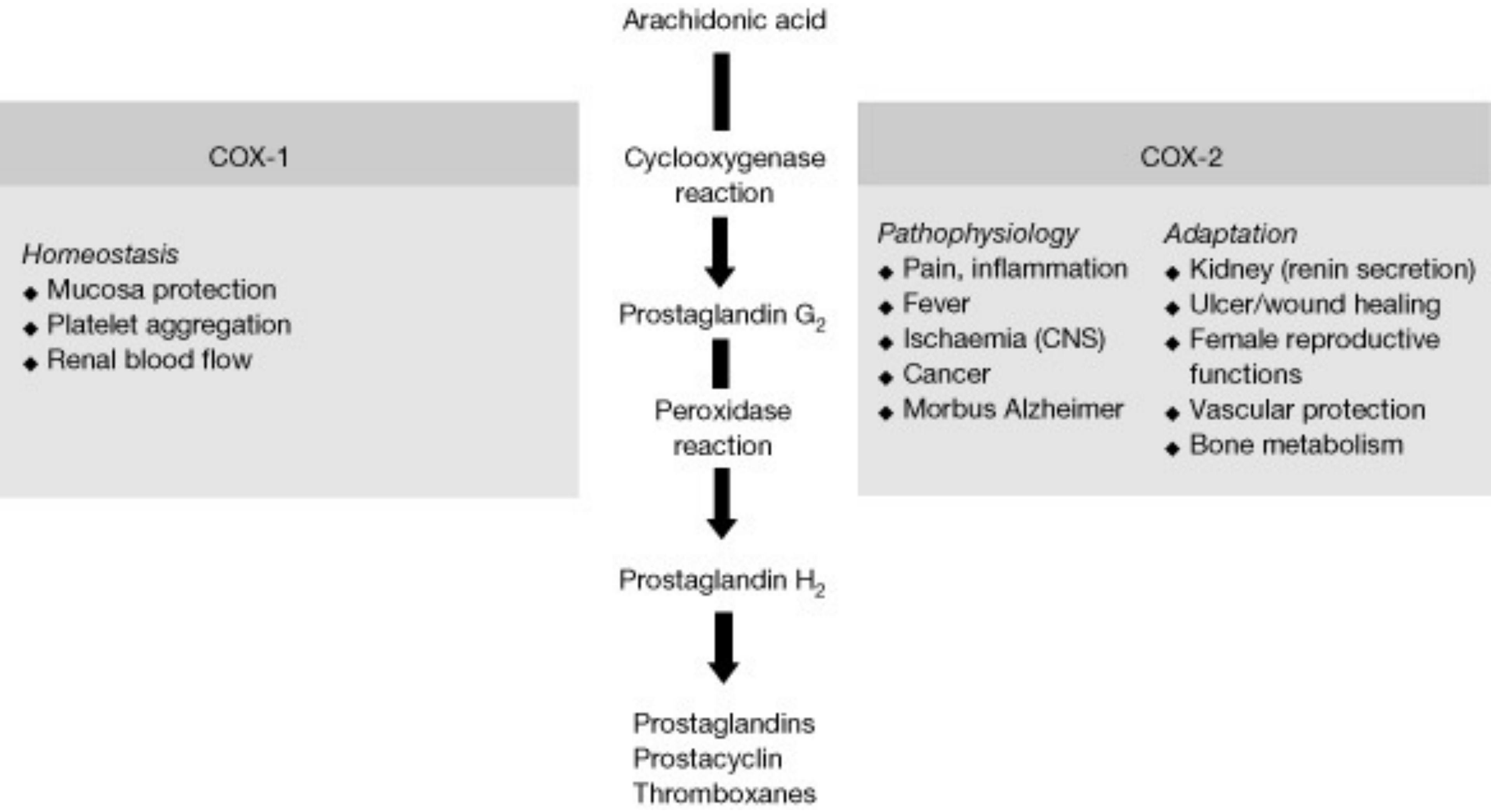
# 解熱性止痛劑
## 作用機轉

- 抑制環氧化酶(cyclooxygenase)，而降低前列腺素(PG)和Thromboxame的合成

# *Mechanism of NSAIDs*




*Med Inflamm.* 1996
*Inflamm Res.* 1995




Adapted from LUPUS

# ROLE OF PROSTAGLANDINS

## Pathologic

Fever
Asthma
Ulcers
diarrhea
Dysmenorrhea
Inflammation
Bone erosion
Pain

## Physiologic

Temperature control
Bronchial tone
Cytoprotection
Intestinal mobility
Myometrial tone
Semen viability

# Function of prostaglandins in inflammation

## $PGE_2$, $PGI_2$

*Vasodilation

*Act synergistically with other mediators such as histamine, complement, or LTB4

*Bronchodilation

*Inhibition of platelet aggregation

## $TXA_2$

*Promotion of platelet aggregation

# FUNCTIONS OF COX

## COX-1

Constitutively expressed

Housekeeping function

Present in every organ such as stomach, intestine, kidney, platelets, vascular endothelium

## COX-2

Inducible and present in:

Inflammatory and neoplastic sites, also in kidney, uterus, ovary, brain, small intestine

# FUNCTIONS OF COX

## COX-1

- **Homeostatic**
  - Protection of gastric mucosa
  - Platelet activation
  - Renal functions
  - Macrophage differentiation

## COX-2

Pathologic
  - Information
  - Pain
  - Fever
  - Dysregulated proliferation
- Tissue Repair
- Physiologic
  - Reproduction
  - Renal functions
  - Other (see text)
- Development
  - kidney

# 解熱性止痛劑
## 抗發炎作用

- 抑制發炎組織前列腺素的合成，可用於風濕性關節炎的病患
- 藥效比類固醇藥物弱

# 解熱性止痛劑
## 退熱效應

- 不影響正常人的體溫
- 外來物(細菌、微生物)入侵人體後，所產生的熱原會影響下視丘的體溫調控中心，使體溫升高。
- 此發燒反應與前列腺素的增加有關
- Aspirin可抑制前列腺素的合成與釋放，而防止生溫作用。

# Pharmacology of NSAIDS

- Good absorption
- Hepatic metabolism
- Highly protein bound
- Both enterohepatic and renal excretion
- Variable half life

# Half-life of NSAID

## SHORT HALF LIFE

- ✓ More rapid effect and clearance
- ✓ IBUPROFEN, DICLOFENAC, INDOMETHACIN,

## LONGER HALF LIFE

- ✓ LIFE-Slower onset and slower clearance
- ✓ NAPROSYN, CELOCOXIB, NABUMETONE, PIROXICAM

| TABLE 35.2 HALF-LIVES OF NSAIDs | | | |
|---|---|---|---|
| **Short (<6h)** | | **Long (>12h)** | |
| **NSAID** | **Half-life (h)** | **NSAID** | **Half-life (h)** |
| Aspirin | 0.25 | Azapropazone | 15.0 |
| Diclofenac | 1.1 | Carprofen | 12.0 |
| Etodolac | 6.0 | Celecoxib | 12.0 |
| Fenoprofen | 2.5 | Diflunisal | 13.0 |
| Flufenamic acid | 1.4 | Fenbufen | 11.0 |
| Flurbiprofen | 3.8 | Meloxicam | 20.0 |
| Ibuprofen | 2.1 | Nabumetone | 26.0 |
| Indomethacin | 4.6 | Naproxen | 14.0 |
| Ketoprofen | 1.8 | Oxaprozin | 58.0 |
| Mefenamic acid | 2.0 | Phenylbutazone | 86.0 |
| Pirprofen | 3.8 | Piroxicam | 57.0 |
| Suprofen | 2.5 | Rofecoxib | 17 |
| Tolmetin | 1.0 | Salicylate | 2.0–15.0 |
| Tiaprofenic acid | 3.0 | Sulindac | 14.0 |
| | | Tenoxicam | 60.0 |

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# Toxicity of NSAID

- GASTROINTESTINAL
- RENAL
- HEMATOLOGIC
- CNS
- HEPATIC
- SKIN
- ALLERGIC

# NSAIDS-HEMOSTASIS

- Impaired platelet aggregation
- Anti-coagulation effects
- Prolonged bleeding time
- COX-2 inhibitors

# 解熱性止痛劑
## 副作用

- 胃腸道副作用
  - 刺激化學接受器而引起噁心、嘔吐
  - 刺激胃部黏膜及增加胃酸分泌而引發潰瘍、胃出血
  - 所導致胃腸道的傷害是因為前列腺素受到抑制的結果，而非這類藥物直接侵蝕性的作用

# NSAID-Induced GI Mucosal Injury

## Upper GI

- **GERD**
- **Subepithelial petechial hemorrhages**
- **Erosions**
- **Ulcers**
  - **Stomach > duodenum**
- **Bleeding**
  - **Stomach » duodenum**
- **Perforations/obstruction**

## Small Intestine

- Ulcers
- Strictures
- Diaphragms
- Enteropathy

## Colon

- Colitis, ulcers
- Strictures
- Diverticular bleed or perforation
- Collagenous colitis
- Relapse of IBD

# Upper GI effects of NSAIDS (summary)

- **COX-2 inhibitors reduced NSAIDS' GI toxicity.**
- **COX-2 inhibitors have been widely used by patients not at high risk of NSAIDS' GI effects**
- **Limitations of COX-2 Inhibitors:**
  - No great need for COX-2s in patients at low GI risk
  - No GI benefit in patients concurrently taking aspirin
  - CV concerns exist for some patients

# Upper GI effects of NSAIDS (summary)

- Strategies to reduce risk of GI effects of NSAIDS should focus on patients at greatest GI risk
- COX-2 inhibitors are an attractive option from the GI perspective.
- Patients who take low-dose aspirin or when CV concerns exist → may consider other strategies to reduce NSAIDs' GI effects

# 解熱性止痛劑
## 副作用

- 呼吸中樞副作用
  - 在治療劑量內，可刺激呼吸中樞使換氣速率增加，導致二氧化碳的濃度減少而造成呼吸性鹼中毒
  - 達毒性劑量時，可抑制呼吸中樞而導致血漿二氧化碳的濃度上升，又因腎血流減少，造成體內代謝性的酸性物質積蓄，而產生代謝性酸中毒

# 解熱性止痛劑
## 抑制血小板凝集

- 會抑制thromboxame A2的形成，而延長流血時間、增加出血

# CNS toxicity of NSAID

- Headache
- Confusion
- Dizziness
- Mood alteration, depression
- Aseptic meningitis

# Liver toxicity of NSAID

- Idiosyncratic severe hepatitis
- Fatal hepatitis
- cholestasis

# 解熱性止痛劑
## 副作用

- 腎毒性
  - 前列腺素PGE1和PGI2是分別由腎隨質和腎絲球所合成的強力血管舒張劑，並且與腎臟血流的控制，以及鹽和水的排泄作用相關
  - 前列腺素的合成受抑制時，可能導致鈉滯留、腎血流減少、甚至腎衰竭
  - 能引起腎炎和高血鉀症。顧常年濫用止痛藥，與慢性腎衰竭有關

# Renal toxicity of NSAIDS

- DECREASED RBF: decreased renal PG
- RISK FACTORS: volume depletion, renal liver diseases, vascular disease
- EDEMA, HBP, INCREASED CREATININE
- NEPHROTIC SYNDROME: interstitial nephritis
- ELECTROLYTE IMBALANCE: K+
- ATTENUATION OF BP MEDS
- PAPILLARY NECROSIS
- STONES

# NSAIDS: hypersensitivity

- Urticaria
- Anaphalaxis
- Bronchospasm
- Nasal polyps, asthma

# NSAIDS and cancer

- Decrease in colon cancer
- Decrease number and size of adenomas in patients with history of familial adenomas
- COX-2 inhibitors approved in familial polyposis

# Questions that patients will ask

- GI intolerance, GI ulceration, bleeding
- Edema
- Elevated BP
- CNS side effects
- Rashes and allergic reaction
- Liver toxicity

# ***Glucocorticoids*類固醇**

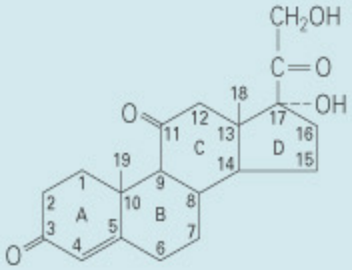
# 有關類固醇的二三事??

- 醫師真沒醫德,沒良心,開類固醇給你吃
- 夭壽!
- 小心洗腎
- 沒知識
- 類固醇是維骨力?
- 類固醇是美國仙丹,我要美國進口的?
- 類固醇會上火?

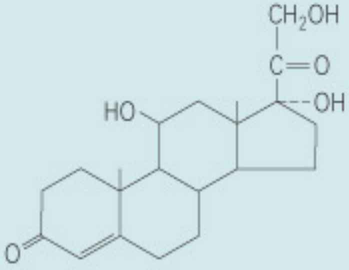
# Glucocorticoids: Indications

- Suppression of the inflammatory cascade
- Modification of the immune response

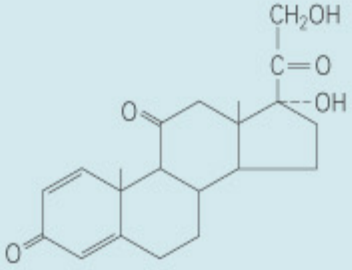
## STRUCTURE OF SOME NATURAL AND SYNTHETIC GLUCOCORTICOIDS



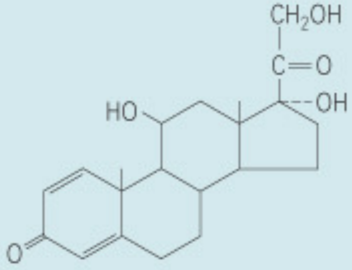
Cortisone (compound E)



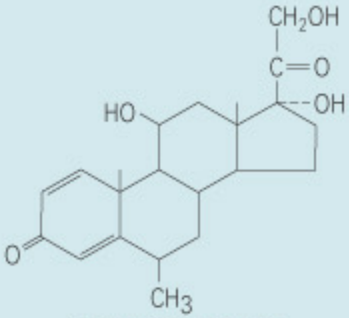
Cortisol (hydrocortisone, compound F)



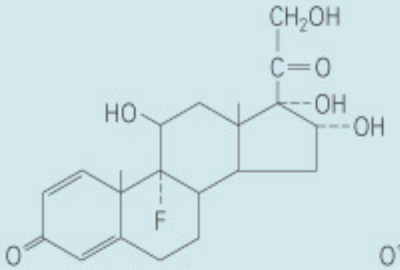
Prednisone



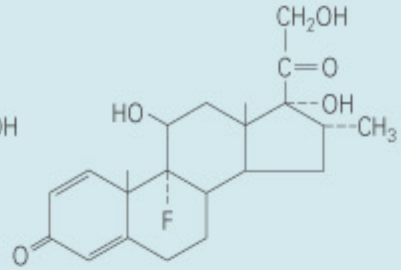
Prednisolone



Methylprednisolone



Triamcinolone



Dexamethasone

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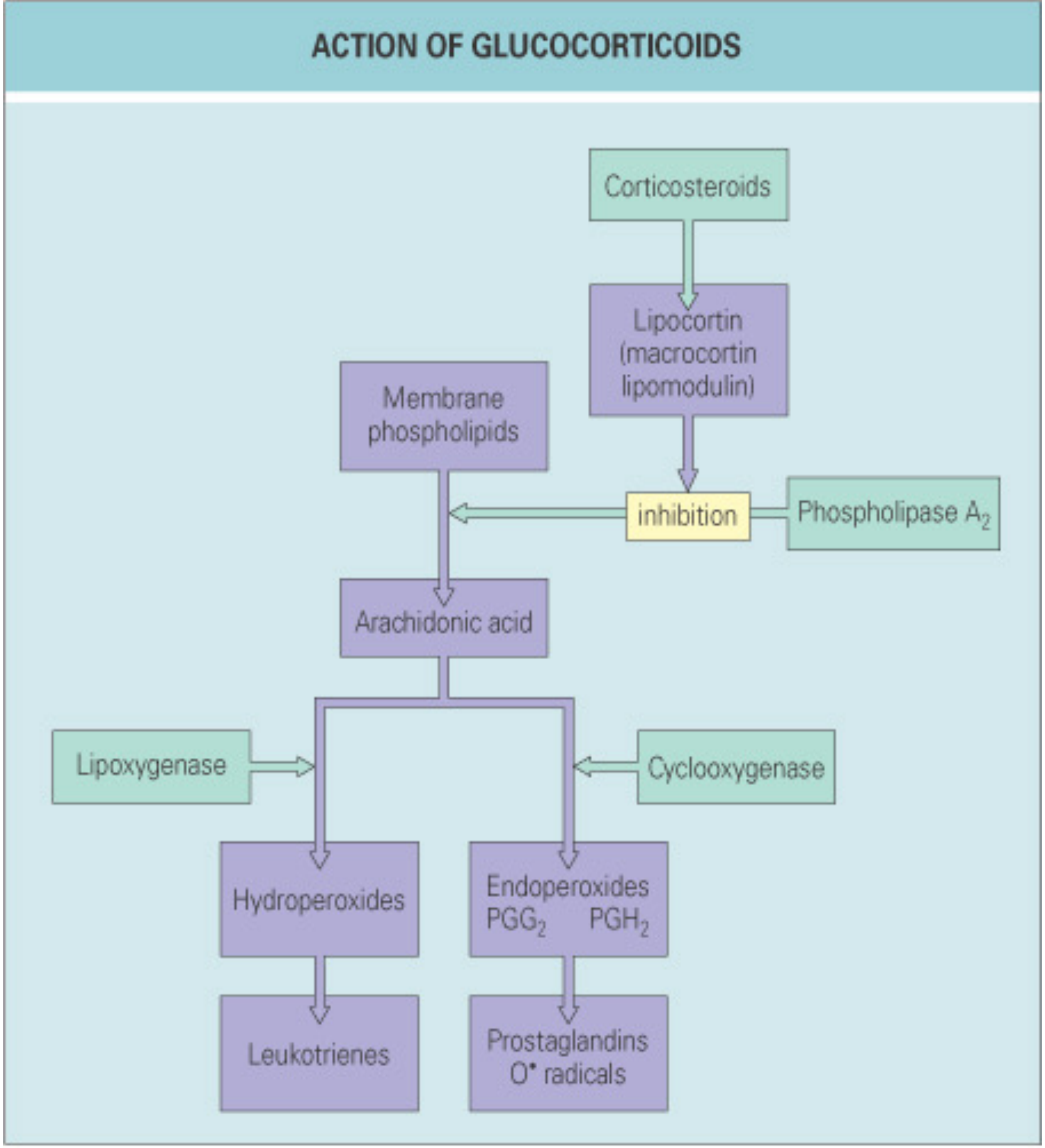


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# Glucocorticoids: methods of administration

- ✓ Intrasynovial therapy(needle injection into joint, bursa or tendon sheath)
- ✓ Oral or alimentary therapy
- ✓ Parenteral: intramuscular and intravenous

# Which clinical baseline should be established before instituting corticosteroid therapy

- Some chronic infection (obtain a chest X-ray and a tuberculin skin test
- A baseline fasting glucose for glucose intolerance
- To assess one's risk for osteoporosis-related problems
- The activity of gastrointestinal erosive disease
- Cardiovascular disease and hypertension
- MiniMental status examination

# Important drug properties to consider when deciding which corticosteroid preparation to use

- ✓ Biological half-life
- ✓ Mineralocorticoid effects
- ✓ Biological equivalency
- ✓ Formulation or the preparation
- ✓ Cost of the medication

# Adverse consequences of corticosteroid therapy(1)

- Glucose intolerance
- Growth suppressions( less if dose<0.5 mg/kg)
- Osteonecrosis
- Cataract formation (even at prednisone 5mg daily)
- Skin disorders (bruising, striae, delayed wound repair)
- Peptic ulcer disease (dose>10 mg/d with NSAID)

# Adverse consequences of corticosteroid therapy (2)

- Obesity
- Infection (dose > 0.3 mg/kg)
- Hirsutism
- Abnormal menstruation
- Depressed hormone levels( TSH, testosterone, FSH/LH)
- Mental disturbance (doses> 30 mg/d)
- Muscle weakness (doses> 10-20 mg/d)
- Osteoporosis (doses> 5-7.5 mg/d)

# Glucocorticoids: dose

- Low dose: < 15 mg/d
- Medium dose: 15-40 mg/d
- High dose: > 40 mg/d

# Basic measures that should be done for patients receiving glucocorticoids

- Prescribe steroid at the lowest possible dose and discontinue as soon as the disease activity permits
- Encourage physical activities and avoid immobilization (helps prevent myopathy)
- Prescribe calcium to achieve a minimum intake of 1500 mg/d
- Supply vitamin D at a minimum of 400 IU/d
- Consider bisphosphonate therapy implementation (if > 7.5 mg/day for > 3 months)
- Patient education concerning the adverse effects of therapy

# Disease modifying anti-rheumatic drugs (DMARDs)

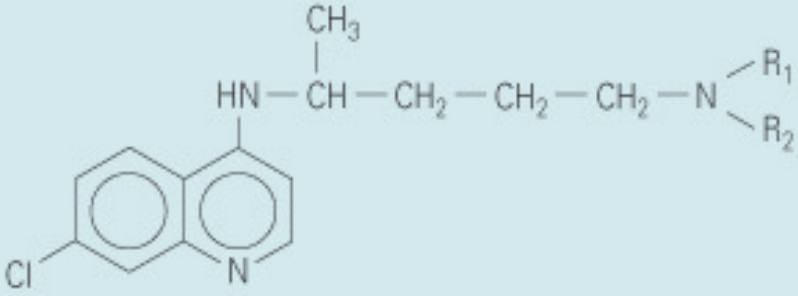
# Hydroxychloroquine

- Alkalinizing lysosomes and interfering with protease function and release.
- Inhibition of IL-1 release and RNA and DNA synthesis
- Effects on lysosome function and antigen processing in lymphocytes, macrophages, fibroblasts, and polymorphs.

# Hydroxychloroquine

- Decreased IL-1
- Metabolized in the liver and then renally excreted
- GI upset, headache, rash, retinopathy

## ANTIMALARIALS USED IN RHEUMATIC DISEASES




| | $R_1$ | $R_2$ |
|---|---|---|
| Chloroquine | $CH_2CH_3$ | $CH_2CH_3$ |
| Hydroxychloroquine | $CH_2CH_3$ | $CH_2CH_2OH$ |
| Desethylchloroquine | $CH_2CH_3$ | H |
| Desethylhydroxychloroquine | H | $CH_2CH_2OH$ |
| Bisdesethylchloroquine | H | H |

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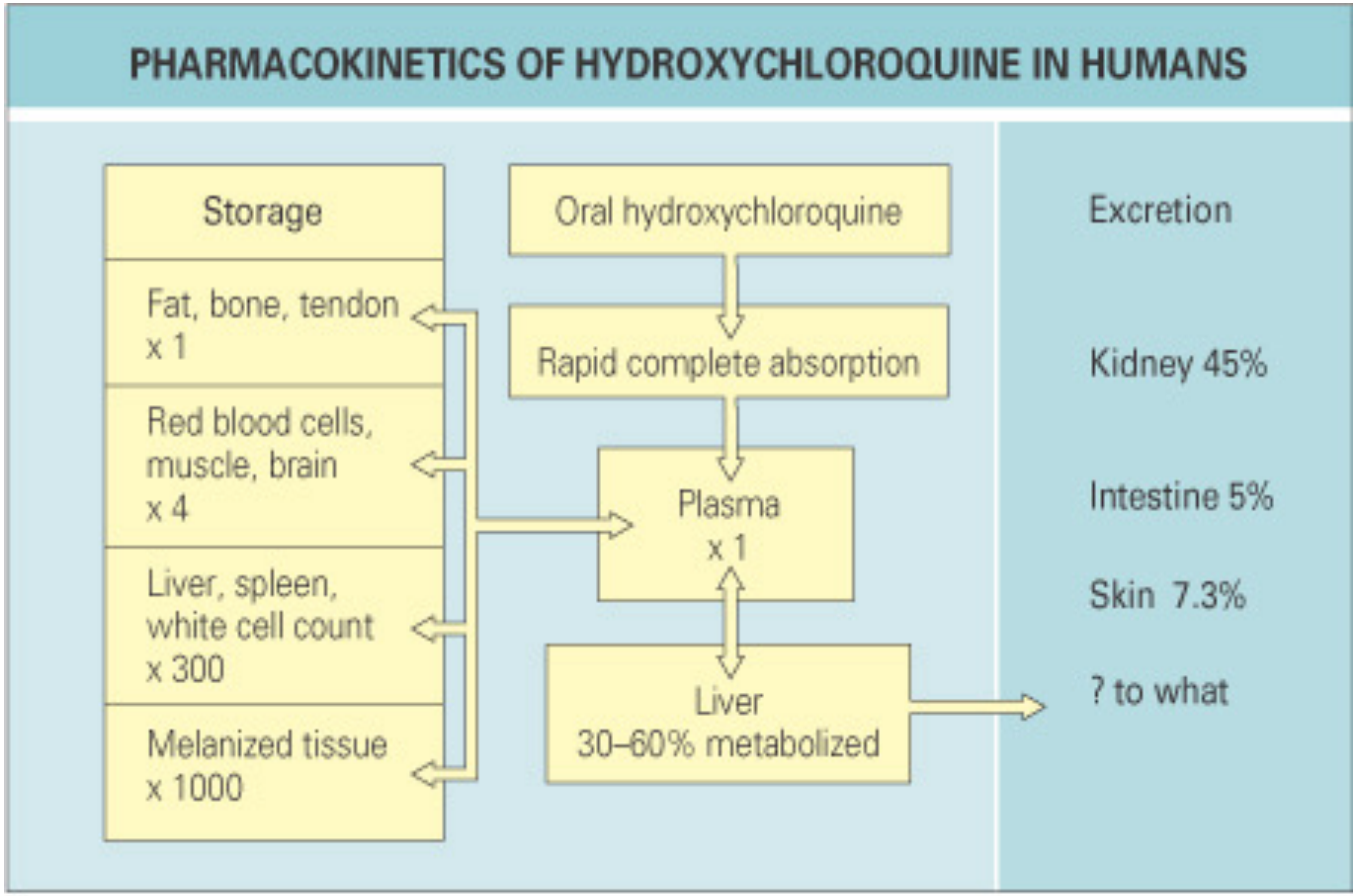


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**TABLE 38.1 TOXICITY OF ANTIMALARIALS**

| Organ | Side effect |
|---|---|
| Gastrointestinal tract | Nausea, abdominal discomfort, diarrhea |
| Skin | Rash, depigmentation |
| Eye | Blurring of vision, rarely retinopathy |
| Central nervous system | Tinnitus, headache |
| Muscle | Myopathy |
| Pregnancy | Crosses placenta and risk of fetal abnormalities |

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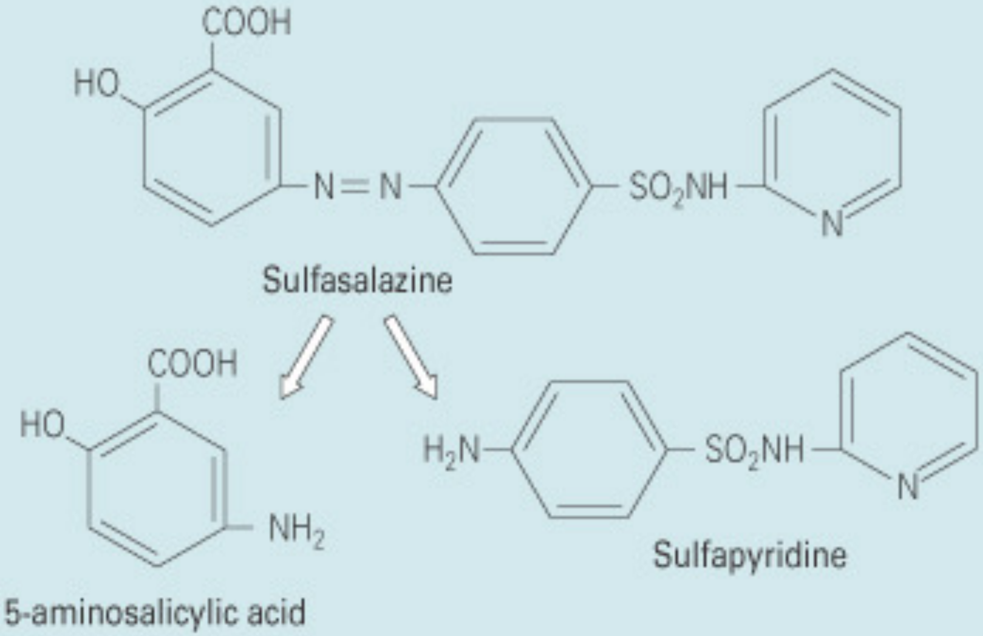
# Sulfasalazine

- Scavenge proinflammatory reactive oxygen species.
- Lowers prostenoid levels (e.g. leukotriene B 4 )
- Reduced numbers of activated lymphocytes Sulfapyridine and 5-aminosalicylic acid liberated from sulfasalazine in the colon.

# Sulfasalazine

- Sulfapyridine is metabolized by N 4 - acetylation, ring hydroxylation and subsequent gluconuration
- Rash, GI upset, marrow suppression, hepatotoxicity, orange urine/tears, reversible decreased spermatogenesis, rarely renal failure, increased ANA titre

## STRUCTURE OF SULFASALAZINE

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| TABLE 39.9 TOXICITY SUMMARY – SULFASALAZINE | | |
|---|---|---|
| **Adverse events** | **Estimated % withdrawals for this reason** | **Clinical management** |
| **Common** | | |
| Nausea/vomiting | 10–15 | Reduce dose<br>Try symptomatic prochlorperazine |
| Upper gastrointestinal tract disturbance | | Slower dose increments<br>Temporary prochlorperazine |
| Rash/mouth ulcers | 6–14 | Reduce dose<br>Symptomatic treatment<br>Withdraw drug if becomes severe/intolerable to patients |
| Abdominal pain | 3–5 | Reduce dose |
| Diarrhea | | Slower dose increments |
| Dizziness/headache | 2 | Reduce dose |
| Malaise/irritability | | Slower dose increments |
| Reversible reduction in sperm count | (Depends on personal circumstances) | Withdraw if patient and partner wishing to start family |
| **Less common** | | |
| Hepatic function abnormality | 0.5–3 | Reduce dose<br>Withdraw treatment if deterioration (tolerate up to 2× upper limit of normal) |
| Leukopenia | 1–3 | *Mild* ($3.0–3.9 \times 10^9$/l): withhold drug, check hematinics, ?rechallenge<br>*Moderate-severe*: stop therapy, treat infection if necessary. Recovery usual in 10 days<br>**Do not rechallenge** |
| Hypogammaglobulinemia | 2–3 | If good response continue therapy: may require i.v. IgG if evidence of infections. |
| **Extremely rare** | | |
| Heinz body anemia | <0.5 | Withdraw treatment |
| Pneumonitis | <0.1 | |
| Lymphadenopathy | <0.1 | |
| Fever/rash/hepatic reaction | <0.1 | |
| Drug-induced systemic lupus erythematosus | <0.1 | |

Desensitization is not effective in reducing incidence of side-effects.

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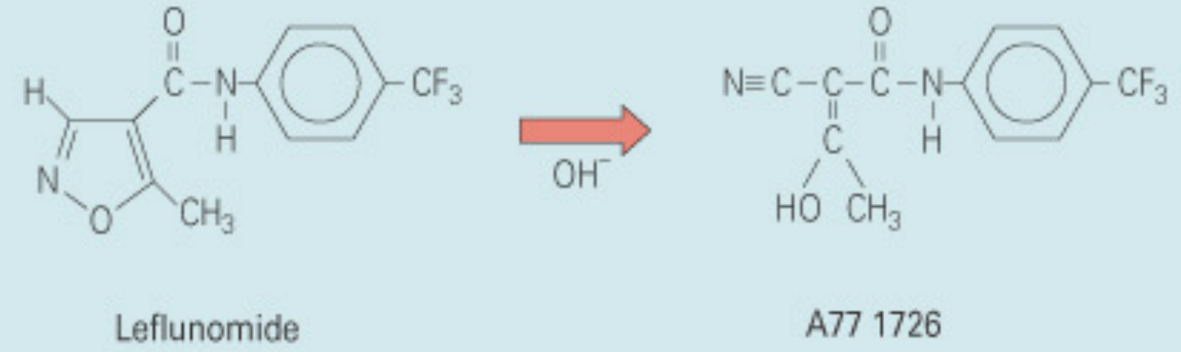
# Leflunomide

- Active metabolite inhibits hydroorotate dehydrogenase inhibiting cell cycle of activated cells
- Decreased lymphocyte immune functions.
- Inhibition of antigen processing

# Leflunomide

- The active metabolite is further metabolized and then renally excreted
- Side-effects: hypertension, leucopaenia, hepatic impairment, GI upset, headache, hair loss, rash
- The incidence of toxicity appears to be most common during the first 2–4 weeks of therapy and may be related to the loading dose.

## STRUCTURE OF LEFLUNOMIDE AND ITS ACTIVE METABOLITE

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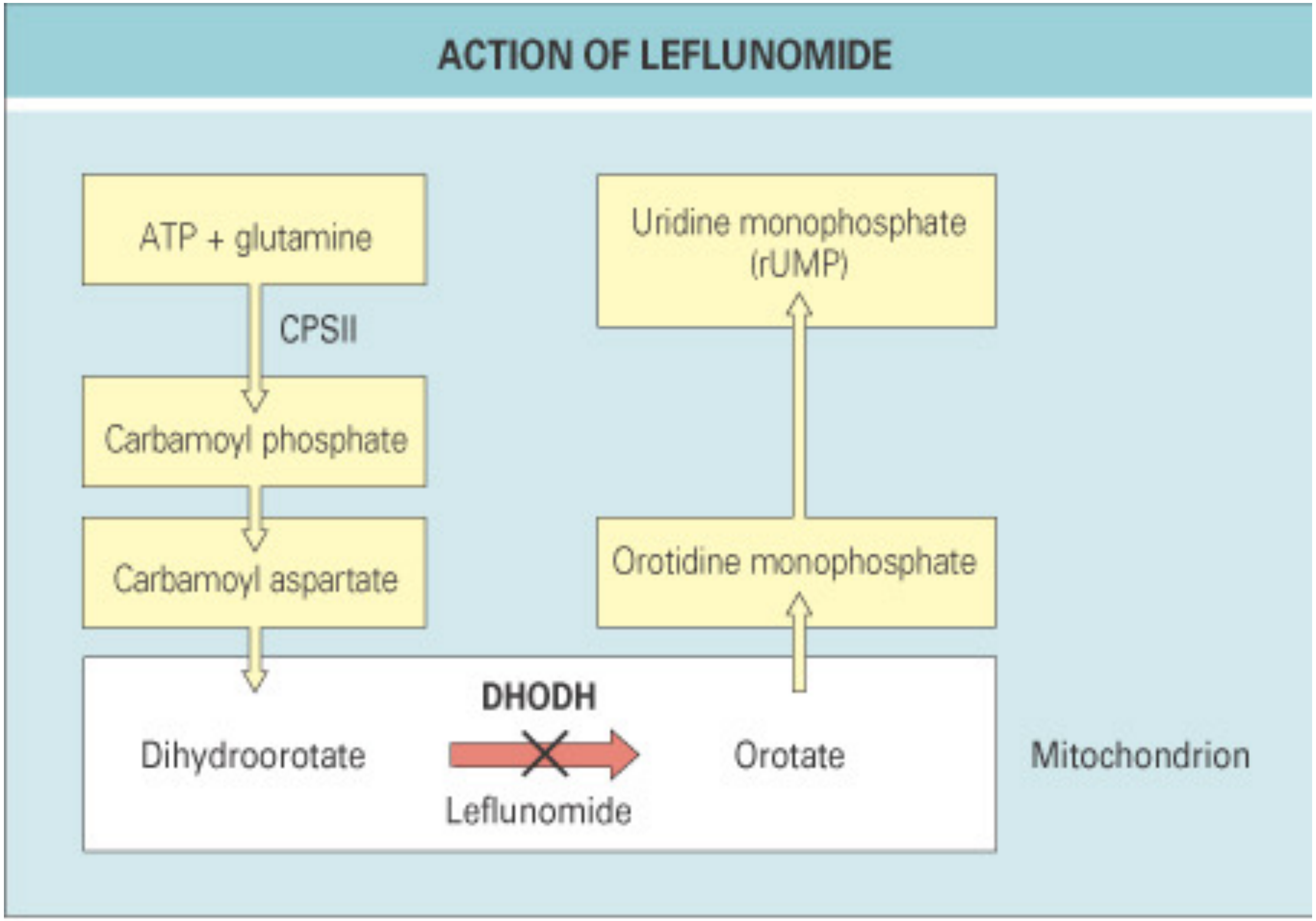


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## TABLE 41.2 ABNORMAL LIVER FUNCTION TESTS WITH LEFLUNOMIDE

| | Incidence (%) | | |
|---|---|---|---|
| Study and treatment arm | >1.2 × ULN | >2 × ULN | >3 × ULN |
| Strand *et al.*[17] | | | |
| Leflunomide | 28.6 | 11.0 | 4.4 |
| Methotrexate | 20.3 | 9.3 | 2.7 |
| Placebo | 9.3 | 2.5 | 2.5 |
| Emery *et al.*[21] | | | |
| Leflunomide | 21.4 | 7.0 | 2.6 |
| Methotrexate | 48.4 | 31.5 | 16.7 |
| Smolen *et al.*[22] | | | |
| Leflunomide | 18.8 | 2.3 | 1.5 |
| Sulfasalazine | 14.3 | 6.0 | 1.5 |
| Placebo | 12.0 | 1.1 | 1.1 |

Abnormalities in ALT (SGPT) in phase III leflunomide studies are listed. ULN, upper limit of normal.

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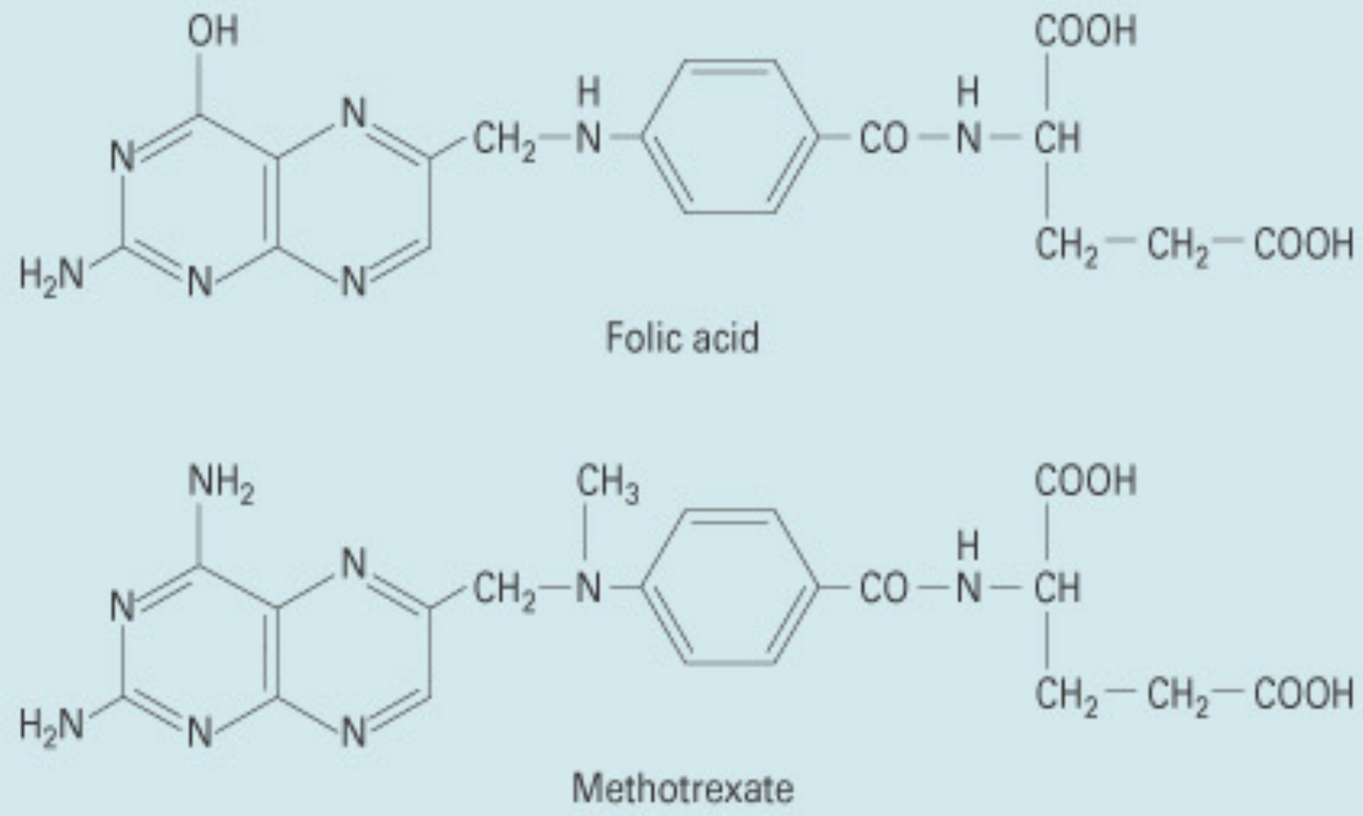
# Methotrexate

- Inhibits 5-aminoimidazole-carboxamide-ribonucleotide-transformase increasing adenosine levels.
- Inhibits dihydrofolate reductase leading to lack of purine nucleotides
- Reduced leukocyte trafficking, inhibition of T-cell and macrophage function.
- Decreased IL-1 and IL-2 production

# Methotrexate

- MTX is normally given orally once a week, but can also be given parenteraly if there is concern regarding bioavailibity or in order to prevent gastric toxicity
- The dose of MTX must be reduced in renal impairment and its use is contraindicated in the presence of significant renal disease.
- Concomitant NSAIDs reduce renal clearance of MTX.
- MTX and its metabolites mainly eliminated via the kidney
- Marrow suppression, hepatic impairment, pneumonitis, GI upset, stomatitis, headache, fatigue, malaise

## CHEMICAL STRUCTURES OF FOLIC ACID AND METHOTREXATE

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## TABLE 40.2 ADVERSE EVENTS ASSOCIATED WITH LOW-DOSE METHOTREXATE

**Gastrointestinal**
- Stomatitis
- Anorexia
- Nausea
- Vomiting
- Abdominal cramping

**Hepatic**
- Macrovesicular steatosis
- Nuclear variability
- Chronic portal inflammation
- Focal necrosis
- Fibrosis
- Cirrhosis

**Pulmonary**
- Acute interstitial pneumonitis
- Interstitial fibrosis
- Non-cardiogenic pulmonary edema
- Pleuritis
- Pleural effusion
- Pulmonary nodules

**Hematopoietic**
- Macrocytosis
- Neutropenia
- Thrombocytopenia
- Pancytopenia

**Cutaneous**
- Rash
- Alopecia
- Actinic keratosis

**Central nervous system**
- Headaches
- Neurocognitive impairment

**Neoplasia**
- Lymphoma
- Leukemia

**Other**
- Nodulosis
- Osteopathy
- Teratogenesis and/or fetal loss

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# D-penicillamine

- Exchange reactions in or on cell surface receptor sulfydryl groups.
- Inhibits binding of transcription factor AP-1
- Modulates activities of T-cells, NK cells, monocytes, and macrophages

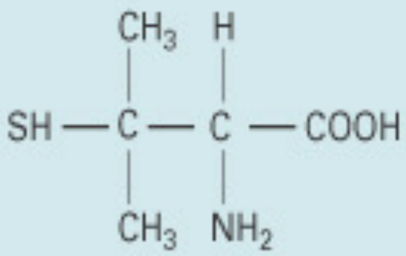
# D-penicillamine

- Cleared largely through oxidation to form disulfides with plasma albumin, L -cystine, homocysteine and itself.
- Patients with impaired sulfoxidation status have increased risk of toxicity
- Nausea, rash, marrow suppression, proteinuria, haematuria, haemolytic anaemia, lupus-like syndrome, myasthenia gravis-like syndrome

# D-penicillamine

- Mild proteinuria is common (30 per cent) and may resolve despite continued treatment.
- Heavy proteinuria and nephrotic syndrome due to membranous glomerulonephritis (GN) may occur and can persist for months or years after cessation of drug.
- DPA can induce Goodpasture's syndrome or systemic lupus erythematosus (SLE), both of which can cause rapidly progressive (crescentic) GN indicated by the presence of haematuria

## CHEMICAL FORMULA OF PENICILLAMINE



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## TABLE 38.4 SIDE EFFECTS OF D-PENICILLAMINE

| Organ | Side effect |
|---|---|
| Skin and mucous membranes | Rash, mouth ulceration, pemphigus |
| Gastrointestinal tract | Loss of taste (early phase of therapy), nausea and vomiting |
| Blood | Thrombocytopenia and neutropenia, occasional marrow aplasia |
| Renal | Proteinuria and hematuria, glomerulonephritis, occasional nephrotic syndrome |
| Muscle | Myasthenia gravis and myositis |
| Auto-immune | Drug-induced SLE |
| Lung | Bronchiolitis obliterans (rare) |

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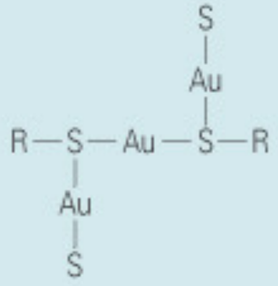
# Gold

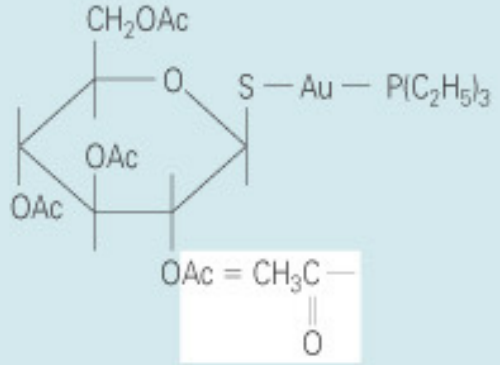
- Inhibits transcription factor AP-1 binding
- Formation of aurocyanide in polymorphonuclear cell phagocytosis
- Effects on polymorphonuclear cell, monocyte and macrophage phagocytosis.
- Decreased HLA class II expression on monocytes.
- Inhibition of synovial cell proliferation.
- Reduced IL-1 induced lymphocyte proliferation
- Mainly excreted unchanged in the urine
- Hypersensitivity reaction, proteinuria, blood disorders

## CHEMISTRY AND REACTIONS OF ANTIARTHRITIC GOLD COMPOUNDS

Polymeric gold complex e.g. sodium aurothiomalate (Autm), aurothioglucose




Auranofin




$$\text{Autm} + \text{RSH} \longrightarrow \text{RSAutm}$$

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## TABLE 38.2 COMMON SIDE EFFECTS OF GOLD COMPOUNDS

| Side effect | Aurothiomalate | Auranofin |
|---|---|---|
| Skin rash | +++ | ++ |
| Mouth ulcers | +++ | +++ |
| Diarrhea | + | +++ |
| Nitritoid reaction | ++ | - |
| Proteinuria | ++ | ++ |
| Marrow suppression (leukopenia, thrombocytopenia) | + | + |

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# Immunosuppressants

# Azathioprine

- Interferes with adenine and guanine ribonucleotides via suppression of inosinic acid synthesis
- Decreased T-cell number (CD8) and function, reduced B-cell function, decreased IL-2
- Cleaved to 6-mercaptopurine (6-MP) which is metabolized to thioinosinic and thioguanylic acid through the action of hypoxanthine phosphoridosyltransferase.
- Two distinct populations of AZA metabolizers: fast and slow, leading to a four-fold variation in the rate of clearance.

# Azathioprine

- The enzyme which metabolizes 6-MP (thiopurine methyltransferase) exhibits genetic polymorphism with a small subset of the population producing low levels leading to increased toxicity (usually bone marrow suppression)
- Hypersensitivity reactions, marrow suppression, hair loss, increased infection risk, nausea

# Azathioprine

- In addition to the principal toxicities of AZA (marrow suppression and gastrointestinal upset), hypersensitivity reactions can occur, which in severe case manifests as multiple organ failure

# Chlorambucil

- Metabolized to phenylacetic acid mustard, which cross-links DNA
- Decreased lymphocyte replication
- Chlorambucil and its metabolites are renally excreted
- Marrow suppression (usually granulocytopaenia or isolated thrombocytopaenia) and infertility.
- Increased risk of cutaneous and haematological malignancy

# Chlorambucil

- Cleaved to 6-mercaptopurine (6-MP) which is metabolized to thioinosinic and thioguanylic acid through the action of hypoxanthine phosphoridosyltransferase.
- Two distinct populations of AZA metabolizers: fast and slow, leading to a four-fold variation in the rate of clearance.

# Chlorambucil

- The enzyme which metabolizes 6-MP (thiopurine methyltransferase) exhibits genetic polymorphism with a small subset of the population producing low levels leading to increased toxicity (usually bone marrow suppression)
- Hypersensitivity reactions, marrow suppression, hair loss, increased infection risk, nausea

# Cyclophosphamide

- DNA cross-linking
- Decreased lymphocyte replication
- Renal excretion of CTX and its metabolites
- Serious side-effects are most common in the first 12 weeks of therapy and include leucopaenia and hepatotoxicity
- Other side-effects: gastrointestinal upset, malignancy, infertility, bone marrow toxicity, and haemorrhagic cystitis

# Cyclophosphamide

- The urological toxicity of CTX is due to its metabolite acrolein, which is excreted in the urine.
- The risk of haemorrhagic cystitis can be reduced by co-administration of mesna with each pulse and assuring adequate patient hydration, neither of which is possible with continuous oral administration.

# Cyclosporin A

- Complexes with cytoplasmic cyclophilin which then binds calcineurin, an intracellular phosphatase
- Decreased IL-2 and hence cellular immune amplification.
- Decreased B-cell response to T-cell dependent antigens.
- Decreased IFN-γ and NK function Metabolized in the liver by cytochrome P-450 mixed-function oxidase to at least 15 metabolites, some of which have immuno-suppressive properties.

# Cyclosporin A

- Elimination is via the biliary system
- Increased serum creatinine and urea, renal impairment, hypertrichosis, tremor, hypertension, hepatic impairment, GI upset
- CYA can commonly reduce glomerular filtration rate (GFR) and should be avoided in patients with pre-existing renal disease.

# Cyclosporin A

- Doses of CYA greater than 5 mg/kg/day or a marked (>50 per cent) increase in serum creatinine have been associated with increased renal damage on biopsy.
- Hypertension can commonly occur, but potassium-sparing antihypertensives should be avoided as CYA can induce hyperkalaemia.
- Calcium-channel blockers may increase CYA concentrations.

# GOUT

- 與血漿中高濃度尿酸有關聯
- 因尿酸(uric acid)結晶鹽在關節處沉積過多所引起的代謝性疾病
- 誘發顆粒性白血球聚集，產生紅、腫、熱、痛的關節發炎反應

# Anti-gout drugs

## Gout

- A systemic disease
  - deficient purine metabolism
  - deposition of uric acid in soft tissue as monosodium urate crystals
- Intra-articular monosodium urate crystals

→ to establish a definitive diagnosis of gouty arthritis

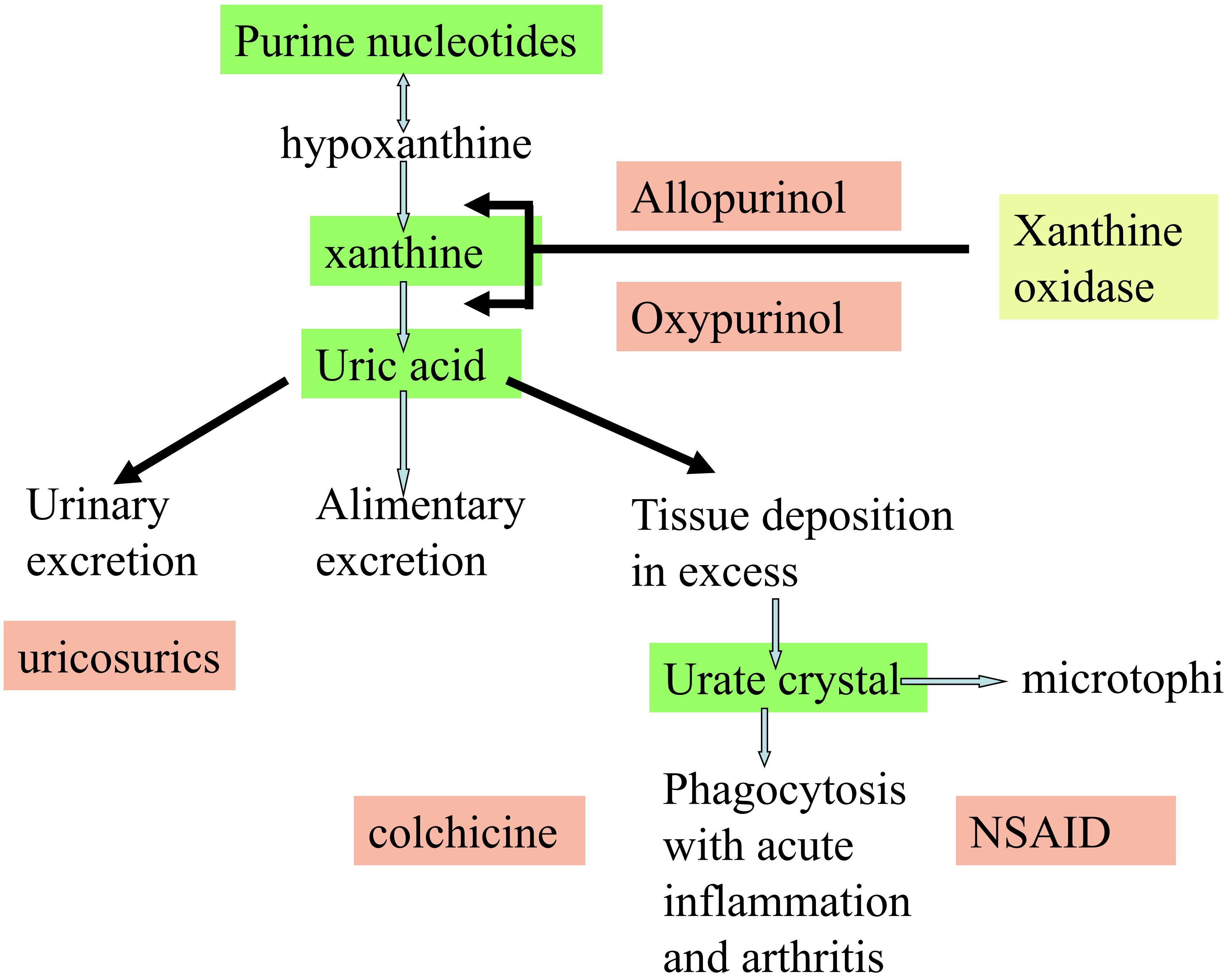
# Causes of hyperuricemia

Table 288-1 -- HYPERURICEMIA: CAUSES AND CLASSIFICATION *

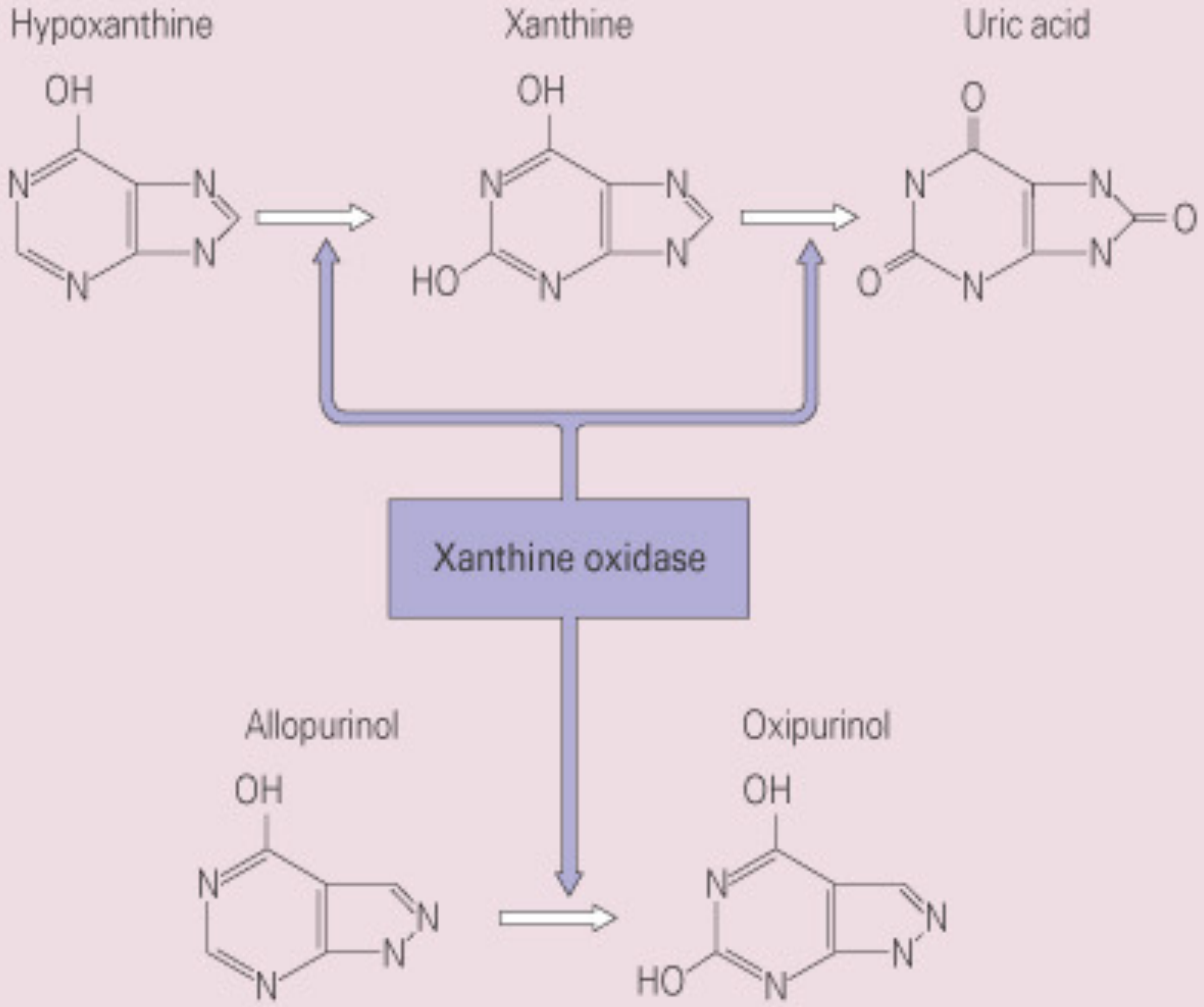
| |
|---|
| **Uric Acid Overproduction** |
| Primary hyperuricemia |
| Idiopathic |
| HGPRT deficiency (partial and complete) |
| PRPP synthetase superactivity |
| Secondary hyperuricemia |
| Excessive dietary purine intake |
| Increased nucleotide turnover (e.g., myeloproliferative and lymphoproliferative disorders, hemolytic diseases, psoriasis, Paget's disease of bone) |
| Accelerated ATP degradation |
| Ethanol abuse |
| Glycogen storage diseases (types I, III, V, VII) |
| Fructose ingestion, hereditary fructose intolerance |
| Hypoxemia and tissue underperfusion |
| Severe muscle exertion |
| ? Hypertriglyceridemia (via metabolism of excess acetate) |

# Causes of hyperuricemia

| Uric Acid Underexcretion |
| --- |
| Primary hyperuricemia |
| Idiopathic (influenced by gender and ethnicity) |
| Familial juvenile hyperuricemic nephropathy |
| Secondary hyperuricemia |
| Diminished glomerular filtration rate |
| Enhanced tubualr urate reabsorption |
| Dehydration |
| Diuretics |
| Insulin resistance (syndrome X) |
| Inhibition of tubular urate secretion |
| Competitive anions (e.g., ketoacidosis and lactic acidosis) |
| Mechanism incompletely defined |
| Hypertension |
| Hyperparathyroidism |
| Hypothyroidism |
| Certain drugs (e.g., cyclosporine, pyrazinamide, ethambutol, low-dose salicylates) |
| Lead toxicity with nephropathy |
| ATP = adenosine triphosphate; HGPRT = hypoxine-guanine phosphoribosyltransferase; PRPP = 5-phosphoribosyl-1-pyrophosphate. |


Purine nucleotides
hypoxanthine
xanthine
Allopurinol
Oxypurinol
Xanthine oxidase
Uric acid
Urinary excretion
Alimentary excretion
Tissue deposition in excess
uricosurics
Urate crystal
microtophi
Phagocytosis with acute inflammation and arthritis
colchicine
NSAID

## SITES OF ACTION OF XANTHINE OXIDASE

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# The management of gout

- **Acute gout**
  - Nonsteroidal anti-inflammatory drugs
  - Colchicine
  - Corticosteroids
  - Do not attempt to modify plasma urate concentrations

# The management of gout

- **Recurrent gout or chronic gout**
  - Reverse factors promoting hyperuricemia
  - Maintain urine output 1400ml/day
  - When asymptomatic, add agent to lower plasma urate concentration (e.g. probenecid or allopurinol)
  - Continue prophylactic doses of colchicine for at least 12 months after normalization of the plasma urate concentration

# 痛風治療藥物

## 秋水仙素(Colchicine)

- 預防及治療急性痛風的首選藥物
- 白血球的微管蛋白(tubulin)結合，防止白血球移動到尿酸堆積處而抑制白血球的吞噬作用，因此減少疼痛和發炎反應
- 不影響尿酸的代謝
- 副作用
  - 噁心、嘔吐、腹瀉、腹痛等胃腸不適
  - 長期使用會禿髮、顆粒性白血球減少。

# Mechanisms of action of Colchicine

- Inhibits phagocytosis by the formation of a tubulin-colchicine dimer which caps the assembly ends of the microtubules
- Alter the motility and adhesion of the neutrophil leukocyte by an effect on the membrane
- Reduces the release of the eicosanoids PGE2 and LTB4 by monocytes and neutrophil leukocytes by inhibiting phospholipase A2
- Affects chemotaxis

# 痛風治療藥物 Allopurinol

- 治療慢性痛風的首選藥物
- 用於高尿酸血症及尿路結石之治療。
- 作用機轉：抑制合成尿酸所需的xanthine oxidase，而降低血中的尿酸值。
- 副作用
  - 過敏反應，胃腸道不適、白血球減少症及下痢。

# Indications for allopurinol use

- Urate overproduction, primary or secondary
- Acute uric acid nephropathy
  - tumor lysis syndrome
- Nephrolithiasis of any type
- Renal impairment (dose 100mg/day per 30ml/min glomerular filtration rate)
- Low urine volume
- 24 hour urinary uric acid > 0.42g (2.5mmol)(an arbitrary value on a low purine diet)
- Intolerance or allergy to uricosuric agents

# 痛風治療藥物
# Probenecid、Sulfinpyrazone

- 抑制腎小管的尿酸再吸收作用，增加尿酸的排泄
- 副作用
  - 過敏反應，胃腸道不適

# Drugs mechanism to normalize hyperuricemia

## Uricosuric drugs

- Facilitate urate excretion by the kidney with an increase in the urate clearance and the fractional excretion of filtered urate
- Especially useful in urate underexcretion

## Xanthine oxidase inhibiting drugs

- Reduce urate production by inhibiting the final enzyme in its pathway
- Especially useful in patients with urate overproduction, both primary and secondary